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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF APPEALS AND INTERFERENCES

In re application of	:	
Kanji TAKADA et al.	:	Group Art Unit.: 1616
Serial No.: 09/787,612	:	Examiner: Sharmila S. Gollamudi
Filed: March 20, 2001	:	

Title: ORAL DRUG DELIVERY SYSTEM FOR ENHANCING THE BIOAVAILABILITY OF ACTIVE FORM OF GLYCYRRHIZIN

BRIEF ON APPEAL

MAIL STOP APPEAL BRIEF – PATENTS
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Further to the Notice of Appeal filed on May 20, 2004, herewith are three copies of Appellants' Brief on Appeal. The attached check includes the statutory fee for the filing of this Brief. The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

This is an appeal from the decision of the Examiner finally rejecting claims 10-19 and 27 of the above-identified application on January 20, 2004.

(1) REAL PARTY IN INTEREST

The real party in interest in the present application is Amato Pharmaceutical Products, Ltd., to whom the present application was assigned on February 15, 2001.

(2) RELATED APPEALS AND INTERFERENCES

There are no known related appeals or interferences.

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(3) STATUS OF THE CLAIMS

Claims 11-18 and 20-27 are pending in the present application. Claims 20-26 were withdrawn from consideration by the Examiner. Claims 10-19 and 27 were rejected. Claims 10 and 19 were cancelled after the Final Action. Claims 11-18 and 27 are on appeal. A petition to rejoin the withdrawn claims is concurrently filed with this Brief on Appeal.

(4) STATUS OF AMENDMENTS AFTER FINAL

Amendments made in the Reply filed April 19, 2004, filed after final rejection, were entered for purposes of appeal. See the Advisory Action mailed May 4, 2004.

(5) SUMMARY OF THE INVENTION

Appellants' invention is directed to a drug delivery system for oral administration of glycyrrhizin. See specification page 1, paragraph [0001]. The oral delivery system contains the glycyrrhizin in a shaped core enclosed in a coating film of ethylcellulose. The nature and thickness of the coating film is such that it collapses selectively in the colon through internal pressure from the peristalsis of the intestine releasing the glycyrrhizin contained therein. See page 11, paragraphs [0033] and [0034]. The delivery system enhances the bioavailability of active glycyrrhizin administered orally to a therapeutically effective level. See page 2, paragraph [0005].

(6) ISSUES

The issue outstanding in this application is whether claims 11-18 and 27 are unpatentable under 35 U.S.C. § 103 over Masanobu (JP 10226650) in view of Takada (US 5,637,319.

(7) GROUPING OF THE CLAIMS

For the purpose of this appeal:

claims 12, 14, 16-18 and 27 are considered to stand or fall together,

claims 13 and 15 are considered to stand or fall together, and

claim 11 stands alone.

(8) APPELLANTS' ARGUMENTS

Issue 1)

Claims 11-18 and 27 were rejected as allegedly unpatentable over Mansanobu, JP 10226650, in view of Takada, US 5637319. Appellants urge that the references do not render the claimed invention obvious to one of ordinary skill in the art and, thus, that the rejection should be reversed.

Masanobu on page 13, in the paragraph labeled [0025], describes the invention taught by the reference as

> The preparation of the present invention comprises glycyrrhizin or a salt thereof and a middle-chain fatty acid or a salt thereof as absorption promoter solubilized in a solubilizing agent, and an enteric coating film applied thereon.

Nowhere does Masanobu describe the invention of the reference as containing "glyceride." Compare claims 13 and 27 on appeal. See also the discussion below regarding the background discussed in the reference. The Office Action alleges that the reference teaches an oral preparation containing glycyrrhizin and a middle chain fatty acid (capric acid), a solubilizing agent such as propylene glycol, polyethylene glycol, or nonionic surfactant. Applicants agree with these allegations, but note that glyceride is not mentioned in the allegations. Masanobu does not teach that the invention described therein contains glyceride.

Masanobu describes various prior art and on page 5, in the first paragraph, describes broadly a composition of glycirrhizin and a fatty acid glyceride which is coated with an enteric film. This disclosure however is not the invention of Masanobu and, also, is very broad. This disclosure may contain embodiments wherein the core material may possibly overlap the core material of the present invention if all the right choices are made within the broad disclosure, for which choices no motivation is present. However, that is not enough or adequate to support an obviousness rejection. Also, there is no suggestion to combine these teachings with the actual Masanobu invention used by the Examiner in the rejection. The reference does not teach or suggest a core material that forms a shaped core and also melts at or about the body temperature. No motivation for the required selections is provided by the reference to the presently claimed core.

The invention of the reference is directed to a solubilized form of glycyrrhizin in a composition. Masanobu on page 7, lines 1-6, teaches that

> delivery of a drug and an absorption promoter to the large intestine in solid state was not effective to improve the absorption sufficiently. The present invention has solved this problem by solubilizing the solid drug and absorption promoter in a solubilizing agent.

Thus, not only is there no teaching in the reference to glyceride as part of the reference invention, but also nowhere does Masanobu teach or suggest a shaped core material that is solid and "melts or liquefies at body temperature." Compare claims 13 and 27, on appeal. Instead, the reference teaches that the prior art problems were solved by solubilizing. See for example, the passage on page 7, paragraph labeled [0010], which immediately follows the previously cited passage.

> Solubilization of glycyrrhizin and absorption promoter has been thought very difficult as is apparent from the above-cited prior art ... wherein a lipid emulsion or a complex mixture in lipid is used. The inventors have succeed [sic] the solubilization using the solubilizing agent of the present invention.

Additionally, all the examples of Masanobu according to the invention are in the form of solutions. The comparative examples are pelletized powder, e.g., are solid. See examples and comparative examples. Masanobu teaches that the examples in accord with the invention, e.g., the ones solubilized, exhibited very excellent absorption over the preparations of the comparative examples. See page 22, paragraph labeled [0052]. Thus, contrary to suggesting a solid core that melts or liquefies, it contrasts its invention to such.

Furthermore, even if the core material may solidify a time after the solubilizing takes place, which is not admitted, or taught, or suggested by the reference, it is not enough that Masanobu's product is capable of solidifying, e.g., for example, under very cold temperatures perhaps all things solidify and/or freeze. It is inherent in the instant claims that the shaped core is solid at room temperature and melts or liquefies at body temperature. Masanobu suggests no such composition. The reference must teach or suggest such a limitation.

Additionally, both the invention of Masanobu and the prior art described on page 5 are coated with an enteric coating. Nothing in the reference teaches or suggests that other types of coating would be useful or desired over the disclosed compositions. There is no teaching or suggestion in this reference to motivate one of ordinary skill in the art to use coatings other than enteric. There is no suggestion in Masanobu of a tablet with an ethylcellulose film coating. As discussed below, Takada, the secondary reference, teaches that an ethylcellulose film is insoluble in the body and, thus, is not an enteric coating, which dissolves at certain pH. Note also the

claim language regarding "rupturing" of the ethylcellulose film by application of physical pressure, rather than dissolution, which occurs with an enteric coating.

To summarize, Masonobu falls short in many aspects from teaching the claimed invention, for example, it does not teach or suggest: 1) the presence of glyceride in the core material, 2) that the core material is shaped, 3) that the core material melts or liquefies at the body temperature, 4) that the coating is made of ethylcellulose, or 5) that the coating ruptures by application of physical pressure.

Takada teaches a variety of capsules, one of which is an ethylcellulose capsule. Intestinal pressure controlled preparations are described on column 8, lines 15-27. Takada teaches that

> if the drug is liquid or is used as solution or suspension, (1) coat the inner surface of a whole gelatin capsule with EC by introducing EC solution through a pore made at the top of gelatin capsule followed [sic] rotating the capsule at horizontal position and evaporating the solvent, (2) fill a drug solution dissolved in a solvent such as propylene glycol (PG) into the EC coated gelatin capsule through a pore at the top of the capsule, (3) close the pore by the drop of EC glue.

See column 8, lines 18-27. Thus, if the solution of Masanobu were to be filled into an intestinal pressure-controlled capsule taught by Takada instead of the soft capsule, e.g., use Takada's ethylcellulose capsule in Masanobu's core, said capsule would also contain a gelatin capsule, which is excluded by the claim language. Compare the "consisting of" language of claims 13 and 27, which would exclude a gelatin layer in the capsule.

Takada also teaches that the intestinal pressure-controlled capsule can be formed by "coating the inner or outer surface of a conventional gelatin capsule body and dissolving gelatin in warm water." See column 8, lines 15-18, referring to preparation described as in (A)(1), which is located on column 7, lines 59-64. While the reference does not expressly state on column 8, lines 15-18, that this embodiment applies to solid cores during processing, it appears to be the case in view of the separate treatment of core material that is liquid or is used as solution or suspension. The core material, if a tablet, can be placed into this capsule. See column 7, line 65. Placing Masanobu's core material, which is in the form of a solution, into an ethylcellulose capsule described in this paragraph analogously to a tablet cannot be done unless such solution or suspension is first placed into another capsule, for example, into a soft gellatin capsule to form a tablet. Then, if the solution of Masanobu is already in a soft capsule when placed into an ethylcellulose capsule, the resultant product would be excluded by the present

claims which use the "consisting of" language, because of the presence of a soft capsule in the product obtained by following the teachings of the references.

Nowhere does Takada teach or suggest processing a liquid core material directly (meaning without the presence of a soft or gelatin capsule) into an intestinal pressure-controlled ethylcellulose capsule.

Furthermore, no motivation is present for combining the teachings of Masanobu and Takada. Masanobu is directed to an oral preparation with an enteric coating that delivers glycyrrhizin that is in a solution. Takada describes a variety of capsules generally, but nowhere does this reference teach or suggest that any or these capsules are or should be interchangeable with enteric coatings, which is the coating Masanobu teaches. Both references lack any teachings that would motivate one of ordinary skill in the art to replace the enteric coating of Masanobu with an ethylcellulose capsule of Takada. Instead, Takada distinguishes an ethylcellulose capsule by stating that it is insoluble in water, which is contrary to how enteric coatings work, i.e., dissolve at a certain pH.

In sum, Masanobu teaches a core material that is different than what is claimed, in at least that it does not teach or suggest: 1) the presence of glyceride in the core material, 2) that the core material is shaped, and 3) that the core material melts or liquefies at the body temperature. Takada teaches nothing with respect to the core material, and thus, even if these references are combined, one of ordinary skill in the art would not achieve the presently claimed invention. Additionally, Masanobu also does not teach or suggest any other coating, but an enteric coating. Takada teaches a variety of coatings, including an intestinal pressure controlled ethylcellulose coating, but does not teach or suggest that this coating is to replace an enteric coating that works in a different way, e.g., dissolves at a certain pH. For the same reason, i.e., the reasons recited in the previous sentence, there is also no motivation to combine these references.

With respect to claim 13 and its dependent claims, in addition to the above reasons, none of the references teach or suggest a device, which contains a powder on the surface of the shaped core. No allegation to that effect has been made; nevertheless, this claim was rejected.

With respect to claim 11, nothing in either reference teaches or suggests a device wherein the amount of glycyrrhizin is in excess of the amount needed for compensating for the hydrolysis thereof by the intestinal flora, and no specific allegation is made to this effect by the Examiner during prosecution. Nevertheless, this claim was also rejected.

Thus, claims 11, 13 and 15 are not obvious for the additional reasons recited above.

(9) CONCLUSION

Applicants submit that for all the foregoing reasons, the combination of these two references do not teach or suggest to one of ordinary skill in the art the claimed invention. Thus, the claims are not obvious under 35 U.S.C. § 103. Reversal of the rejections is therefore respectfully and courteously requested.

Respectfully submitted,

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APPENDIX

11. The device according to claim 27, wherein said amount of glycyrrhizin is in excess of the amount needed for compensating for the hydrolysis thereof by the intestinal flora.

12. The device according to claim 27, wherein said coating film is formed by dipping the shaped core in a solution of ethylcellulose.

13. A device for colon-targeted oral delivery of glycyrrhizin consisting of a shaped core containing an amount of glycyrrhizin, said shaped core being made of a suppository base comprising glyceride that melts or liquefies at the body temperature, a powder on the surface of the shaped core, and a coating film of ethylcellulose enclosing said shaped core and having a film thickness whereby when the device is transported through the digestive tract to the colon, the film enclosing the liquefied core ruptures selectively in the colon by the internal pressure generated by the peristalsis of the intestine.

14. The device according to claim 27, wherein said shaped core further contains an absorption promoter for glycyrrhizin.

15. The device according to claim 13, wherein the powder is talc.

16. The device according to claim 14, wherein absorption promoter is an organic acid, a surfactant, a chelating agent, or a mixture thereof.

17. The device according to claim 27, wherein the device contains 10 to 1,000 mg of glycyrrhizin.

18. The device according to claim 27, wherein the device contains 100 to 800 mg of glycyrrhizin.

27. A device for colon-targeted oral delivery of glycyrrhizin consisting of a shaped core containing an amount of glycyrrhizin, said shaped core being made of a suppository base comprising glyceride that melts or liquefies at the body temperature, and a coating film of ethylcellulose enclosing said shaped core and having a film thickness whereby when the device is transported through the digestive tract to the colon, the film enclosing the liquefied core ruptures selectively in the colon by the internal pressure generated by the peristalsis of the intestine.